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# An Expedient Method for the Synthesis of Acylhydrazones under Microwave Irradiation in Solvent-free Medium

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ABSTRACT

**A simple, efficient and eco-friendly method for the synthesis of acylhydrazones from acylhydrazides and aldehydes under microwave (MW) irradiation was reported, no solvent and catalyst was used. The method is combined with a combinatorial approach and fourteen novel acylhydrazones were synthesized in excellent yields (89–96%) and short reaction times (less than 5 min).**

KEYWORDS

**Acylhydrazides, acylhydrazones, acylhydrazones, microwave, solvent-free.**

Acylhydrazones have been extensively investigated in recent years, as they are associated with various biological activities.[1–5] Acylhydrazones also have interesting analytical properties[6–8] and can be used as ligands in orgamometallic catalysts.[9,10] Their metal complexes usually have more active pharmacological properties.[11–15] The cyclic products of acylhydrazones are an important class of heterocyclic compounds with a wide a range of pharmaceutical and biological activities.[16–18]

Usually, the synthetic method to produce acylhydrazones involves the reaction between acylhydrazides and aldehydes in ethanol at reflux temperature for about 2–3 hours, the solvent is then concentrated, the solid filtered off and recrystallized, giving yields of about 70–80%.

Microwave-assisted heating has been shown to be an invaluable method in synthesis,[19] since it can often dramatically reduce reaction times, typically from days or hours to minutes or even seconds. It can also provide pure products in quantitative yield and selectivity. Some reports have described the synthesis of acylhydrazones and their derivatives under microwave irradiation;[20–22] however, these reactions were carried out either on solid supports or using a solvent in a teflon vessel. Even though the reaction time was shortened (10–20 min), the procedure was even more tedious when using solid support. When a solvent is used, the reaction conditions must be carefully controlled or special apparatus should be used, due to the danger of using organic solvents in microwave irradiation because of their low boiling points and high vapour pressure. Since acylhydrazones are partially soluble in the aldehyde or the aldehyde is absorbed onto the surface of the solid with a reaction occurring at the interphase, the reaction can in principle be performed without an additional solvent. The presence of a solvent could also be deleterious due to dilution of the reactant.

Solvent-free reaction techniques were successfully coupled with microwave synthesis.[19] Additionally, a solvent-free process is less expensive and environmentally more friendly. With the rapid development of combinatorial libraries, in which a systematic system of initial screening of potential activities of compounds are possible, a fast and solvent-free method could be very attractive.

In this paper, we introduce a microwave-assisted solvent-free method for the synthesis of acylhydrazones, which allows for a more rapid and easier procedure. A combinatorial approach was employed which could ultimately accelerate the screening and identification of bioactive acylhydrazones.

Five acylhydrazines reacted with seven aldehydes, respectively, to produce thirty-five corresponding acylhydrazones (see Scheme 1). Several experiments were carried out at various reaction times, power levels, and different ratios of the reactants to establish the optimum reaction conditions. The inside temperature of the MW reaction vessel was also studied (as shown in Table 1). The products were analysed using NMR spectroscopy. The $^1$H NMR spectra of most compounds display two sets of methylene, imine and amide protons signals indicating that both *cis* and *trans* amide conformers were formed. It is known from conventional synthesis that the *cis* isomer is formed in excess.[23] It is expected that the *cis* forms of **A1**–**A4** should be the major product due to the formation of an intramolecular hydrogen bond.[24]

All products were obtained in excellent yields (89–96%) and within minutes (between 1.5–5 minutes). The optimum conditions are presented in the experimental section.

In conclusion, the use of microwave synthesis for the synthesis of acylhydrazones under solvent-free conditions proved to be a fast, efficient, safe and environmentally benign technique with excellent yields. The method can be effectively employed as a combinatorial method. This approach can therefore be applied for the synthesis of many other acylhydrazones with various functional groups.

## Experimental

Melting points were determined with an XRC-1 micro melting point apparatus and are uncorrected. Infrared spectra were recorded on a FTS-40 spectrophotometer using KBr Pellets. $^1$H NMR spectra were measured on a Bruker DPX-400 spectrometer using TMS as internal standard and DMSO-$d_6$ as solvent. Chemical shifts ($\delta$) were expressed in ppm downfield from internal standard TMS and coupling constants $J$ were given in Hz. Elemental analyses were performed on PE-2400 elemental analyser. The MW experiments were carried out in a Galanz domestic microwave oven (750 W).

The experimental data of the novel products are presented

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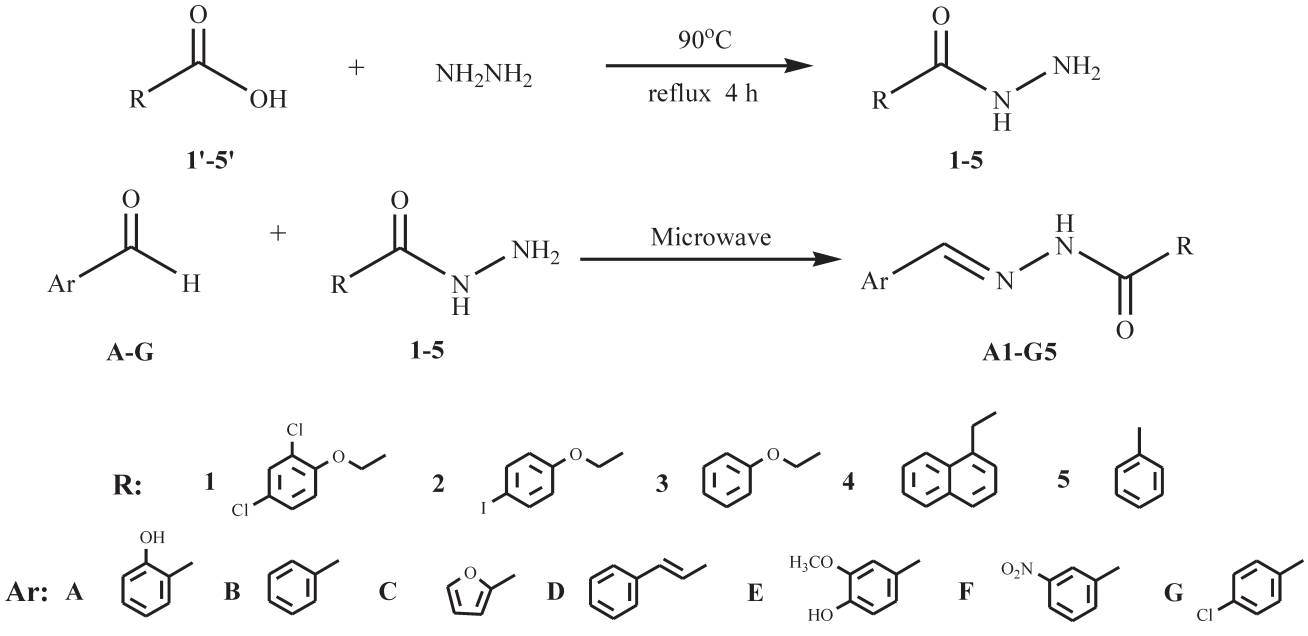


**Scheme 1**

below. The experimental data for the known products (**A1**,[25] **A2**,[26] **A3**,[27] **A4**,[28,29] **A5**,[30] **B1**,[31] **B2**,[26] **B3**,[32] **B4**,[28,29] **B5**,[33] **C1**,[31] **C3**,[34] **C5**,[35] **D3**,[36] **D5**,[37] **E1**,[31] **E4**,[38] **F1**,[39] **G1**,[25] **G3**,[1] **G5**,[40]) are available as supplementary material.

**Synthesis of Acylhydrazides** (1–5)**: Conventional Procedure (Scheme 1)**

The acids (**1′–5′** – 0.1 mol) were dissolved in 0.4 mol 85% hydrazine hydrate. The mixture was heated at 90°C for 4 h and on cooling a white crystal precipitated, which was recrystallized with ethanol-DMF to give the pure acylhydrazide.

**Synthesis of Acylhydrazones** (A1–G5)

*Thermal Conditions*

Equimolar quantities of acylhydrazides and aldehydes were mixed in boiling ethanol for about 2–3 h. The solvent was then concentrated, the solid filtered off and recrystallized with ethanol-DMF to give the pure product.

*Microwave Conditons* (Scheme 1)

General procedure for **A1**–**D5**: 1 mmol of acylhydrazide was put in a test tube, and 1.2 mmol liquid aldehyde was added to it. The test tube was subject to mechanical vibration to ensure maximum dissolution of the solid in the aldehydes. The reaction tubes were then subjected to microwave irradiation (300 W), operated for the specified time (**A1**–**A5**: 1.5 min; **B1**–**B5**, **C1**–**C5**: 2 min; **D1**–**D5**: 2.5 min). After the reaction was completed, the solid was filtered and washed with cool ethanol to yield the pure product. No further purification was required.

*General Procedure for* **E1–G5**

1 mmol of acylhydrazide and 1 mmol of solid aldehyde were thoroughly mixed in an agate mortar. The mixture was put into the microwave oven (495 W) and irradiated for a specific time (**E1–E5**:3 min: **F1–F5**, **G1–G5**: 5 min) to produce the crude solid, which on recrystallization with ethanol-DMF gave the pure product.

*1-[(4-Iodophenoxy)acetyl]-2-furaldehyde-hydrazine* (**C2**). White crystals. M.p. 193–196°C, Yield – 90%. IR (KBr): 3310 (NH), 1682 (C=O), 1486 (C=N) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.52, 11.47 (2s, 1H, N-H), 8.19, 7.86 (2s, 1H, CH=N), 7.81–6.59 (m, 7H, ArH), 5.03, 4.61 (2s, 2H, $CH_2$). Anal. calcd. for $C_{13}H_{11}IN_2O_3$: C, 42.18; H, 3.00; N, 7.57. Found: C, 42.27; H, 3.23; N, 7.49.

**Table 1** The inside temperature of the MW flask as function of time and energy.

| | Time | | | | |
|---|---|---|---|---|---|
| Power | 1.5 min | 2 min | 2.5 min | 3 min | 5 min |
| 300 W | 75°C | 83°C | 99°C | – | – |
| 495 W | – | – | – | 124°C | 143°C |

*1-(1-Naphthylacetyl)-2-furaldehyde-hydrazine* (**C4**). White crystals. M.p. 178–180°C, Yield – 91%. IR (KBr): 3263 (NH), 1671 (C=O), 1481 (C=N) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.63, 11.41 (2s, 1H, N-H), 8.12, 7.99 (2s, 1H, CH=N), 8.07–6.58 (m, 10H, ArH), 4.36, 3.99 (2s, 2H, $CH_2$). Anal. calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.48; H, 4.99; N, 10.29.

*1-[(2,4-Dichlorophenoxy)acetyl]-2-cinnamylidene-hydrazine* (**D1**). White crystals. M.p. 226–228°C, Yield – 90%. IR (KBr): 3369 (NH), 1683 (C=O), 1490 (C=N) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.54, 11.48 (2s, 1H, N-H), 8.01, 7.99 (2s, 1H, CH=N), 7.81, 7.79 (d, 1H, ArCH, $J$=8.8 Hz), 7.59–7.55 (m, 1H, =CH), 7.54–6.88 (m, 8H, ArH), 5.16, 4.75 (2s, 2H, $CH_2$). Anal. calcd. for $C_{17}H_{14}Cl_2N_2O_2$: C, 58.47; H, 4.04; N, 8.02. Found: C, 58.38; H, 3.91; N, 8.29.

*1-[(4-Iodophenoxy)acetyl]-2-cinnamylidene-hydrazine* (**D2**). White crystals. M.p. 240–243°C, Yield – 89%. IR (KBr): 3291 (NH), 1679 (C=O), 1487 (C=N) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.48, 11.43 (2s, 1H, N-H), 8.11, 8.09 (2s, 1H, CH=N), 7.81, 7.78 (d, ArCH, 1H, $J$=9.2 Hz), 6.76–7.55 (m, 1H, =CH) 7.37–6.72 (m, 9H, ArH), 4.99, 4.61 (2s, 2H, $CH_2$). Anal. calcd. for $C_{17}H_{15}IN_2O_2$: C, 50.26; H, 3.72; N, 6.90. Found: C, 50.15; H, 3.94; N, 6.77.

*1-(1-Naphthylacetyl)-2-cinnamylidene-hydrazine* (**D4**). White crystals. M.p. 222–224°C, Yield – 91%. IR (KBr): 3273 (NH), 1670 (C=O), 1400 (C=N) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.59, 11.37 (2s, 1H, N-H), 8.07, 8.05 (2s, 1H, CH=N), 8.01, 7.99 (d, ArCH, 1H $J$=8.0 Hz), 7.92–7.89 (m, 1H, =CH) 7.97–6.98 (m, 12H, ArH), 4.35, 3.99 (2s, 2H, $CH_2$). Anal. calcd. for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.08; H, 5.59; N, 9.16.

*1-[(4-Iodophenoxy)acetyl]-2-[(3-methoxy-4-hydroxy)benzylidene]-hydrazine* (**E2**). White crystals. M.p. 210–212°C, Yield – 90%. IR

(KBr): 3225 (NH), 3590, 3403 (OH), 1666 (C=O), 1488 (C=N) $cm^{-1}$. $^1H$ NMR(400 MHz, DMSO-$d_6$): $\delta$ 11.41, 11.33(2s, 1H, N-H), 9.51, 9.46 (2s, 1H, OH), 8.16, 7.85 (2s, 1H, CH=N), 7.61–6.74 (m, 7H, ArH), 5.10, 4.60 (2s, 2H, $CH_2$), 3.77 (s, 3H, $CH_3$). Anal. calcd. for $C_{16}H_{15}IN_2O_4$: C, 45.09; H, 3.55; N, 6.57. Found: C, 45.28; H, 5.50; N, 6.49.

*1-Phenoxyacetyl-2-[(3-methoxy-4-hydroxy)benzylidene]-hydrazine* (**E3**). White crystals. M.p. 190–192°C, Yield – 95%. IR (KBr): 3247 (NH), 3550, 3435 (OH), 1668 (C=O), 1482 (C=N) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.47, 11.39 (2s, 1H, N-H), 9.52, 9.47 (2s, 1H, OH), 8.10, 7.86 (2s, 1H, CH=N), 7.58–6.77 (m, 8H, ArH), 5.26, 4.74 (2s, 2H, $CH_2$), 3.78 (s, 3H, $CH_3$). Anal. calcd. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.78; H, 5.33; N, 9.49.

*1-Benzoyl-2-[(3-methoxy-4-hydroxy)benzylidene]-hydrazine* (**E5**). White crystals. M.p. 218–220°C, Yield – 94%. IR (KBr): 3211 (NH), 3516, 3331 (OH), 1677 (C=O), 1512 (C=N) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.64 (s, 1H, N-H), 9.51 (s, 1H, OH), 8.32 (s, 1H, CH=N), 7.88–6.81 (m, 8H, ArH), 3.81 (s, 3H, $CH_3$). Anal. calcd. for $C_{15}H_{14}N_2O_3$: C, 69.66; H, 5.22; N, 10.36. Found: C, 69.48; H, 5.40; N, 10.43.

*1-[(4-Iodophenoxy)acetyl]-2-(3-nitrobenzylidene)-hydrazine* (**F2**). Yellow crystals. M.p. 194–196°C, Yield – 90%. IR (KBr): 3306 (NH), 1697 (C=O), 1484 (C=N) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.80 (s, 1H, N-H), 8.89, 8.69 (2s, 1H, CH=N), 8.36–7.55 (m, 8H, ArH), 5.17, 4.67 (2s, 2H, $CH_2$). Anal. calcd. for $C_{15}H_{12}IN_3O_4$: C, 42.37; H, 2.84; N, 9.88. Found: C, 42.58; H, 2.93; N, 9.69.

*1-Phenoxyacetyl-2-(3-nitrobenzylidene)-hydrazine* (**F3**). White crystals. M.p. 160–162°C, Yield – 94%. IR (KBr): 3301 (NH), 1682 (C=O), 1492 (C=N) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.80, 11.79 (2s, 1H, N-H), 8.48, 8.43 (2s, 1H, CH=N), 8.24–6.90 (m, 9H, ArH), 5.16, 4.67 (2s, 2H, $CH_2$). Anal. calcd. for $C_{15}H_{13}N_3O_4$: C, 60.20; H, 4.38; N, 14.04. Found: C, 60.39; H, 4.50; N, 13.88.

*1-(1-Naphthylacetyl)-2-(3-nitrobenzylidene)-hydrazine* (**F4**). White crystals. M.p. 224–226°C, Yield – 91%. IR (KBr): 3274 (NH), 1669 (C=O), 1491 (C=N) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.95, 11.69 (2s, 1H, N-H), 8.50, 8.36 (2s, 1H, CH=N), 8.22–7.42 (m, 11H, ArH), 4.47, 4.06 (2s, 2H, $CH_2$). Anal. calcd. for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61. Found: C, 68.51; H, 4.47; N, 12.49.

*1-Benzoyl-2-(3-nitrobenzylidene)-hydrazine* (**F5**). White crystals. M.p. 202–204°C, Yield – 94%. IR (KBr): 3223 (NH), 1668 (C=O), 1490 (C=N) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 12.09 (s, 1H, N-H), 8.55, 8.53 (2s, 1H, CH=N), 8.24–7.50 (m, 9H, ArH). Anal. calcd. for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.37; H, 4.01; N, 15.77.

*1-[(4-Iodophenoxy)acetyl]-2-(3-chlorobenzylidene)-hydrazine* (**G2**). White crystals. M.p. 206–208°C, Yield – 88%. IR (KBr): 3247 (NH), 1683 (C=O), 1487 (C=N) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.63, 11.60 (s, 1H, N-H), 8.69, 8.28 (2s, 1H, CH=N), 7.96–6.75 (m, 8H, ArH), 5.12, 4.64 (2s, 2H, $CH_2$). Anal. calcd. for $C_{15}H_{12}ClIN_2O_2$: C, 45.47; H, 3.31; N, 7.07. Found: C, 45.53; H, 3.50; N, 6.89.

*1-(1-Naphthylacetyl)-2-(3-chlorobenzylidene)-hydrazine* (**G4**). White crystals. M.p. 236–238°C, Yield – 93%. IR (KBr): 3301 (NH), 1672 (C=O), 1489 (C=N) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.76, 11.51 (2s, 1H, N-H), 8.23, 8.01 (2s, 1H, CH=N), 8.03–7.43 (m, 11H, ArH), 4.44, 4.02 (2s, 2H, $CH_2$). Anal. calcd. for $C_{19}H_{15}ClN_2O$: C, 70.70; H, 4.68; N, 8.68. Found: C, 70.59; H, 4.54; N, 8.79.

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